REMARKS

Claims

Claims 79–83 and 85–86 are currently under examination with claims 1–78 and 84 cancelled without prejudice or disclaimer. Claims 87–112 are added by this paper.

Applicants gratefully acknowledge that the subject matter of claims 77–86 is free of prior art.

New claims

New claims 87–112 are supported by the disclosure contained in Applicants' specification. Aspects of the instant invention are presented in independent claims 87 and 95.

Support for new independent claim 87 can be found at, for example, page 9, lines 10–22 and page 11, lines 3–11; support for new claim 88 can be found at, for example, the paragraph bridging pages 13–14; support for new claim 89 can be found at, for example, the paragraph bridging pages 15–16; support for new claim 90 can be found at, for example, the paragraph bridging pages 24–25; support for new claim 91 can be found at, for example, the paragraph bridging pages 30–31 of the originally-filed specification.

Support for new independent claim 95 can be found at, for example, page 9, lines 10–22 and page 11, lines 12–18; support for new claim 96 can be found at, for example, the paragraph bridging pages 13–14; support for new claim 97 can be found at, for example, the paragraph bridging pages 15–16; support for new claim 98 can be found in, for example, the disclosure contained in Table 2 (pages 18–24); support for new claim 100 can be found at, for example, page 31, lines 15–20 of the originally-filed specification.

Claims 82 and 101, directed to constructs comprising one or more recognition molecules and/or claims 92 and 102, directed to compositions comprising one or more recognition molecules are supported by the disclosure contained in, for example, the paragraph bridging pages 31–32 of the originally-filed specification. A detailed disclosure is provided, for example, in the paragraphs spanning pages 32–38.

New claims 113–116 are supported, at least, by the disclosure contained in Example 5. See also, the paragraphs bridging pages 4 and 5 of the originally-filed specification.

Support for the new claims directed to method(s) for the production or method(s) for the use of the instantly claimed recognition molecules and/or compositions comprising the same can

be found in, for example, the paragraph bridging pages 40–41; page 44, ¶2 of the originally-filed specification; and the disclosure contained in the Examples.

It is respectfully submitted that the new claims do not raise new matter.

Claim amendments

The claims have been amended to recite language in accordance with conventional US practice. New dependencies have been recited, the support for which can be found in the entirety of Applicants' disclosure, as originally-filed. See, the aforementioned remarks. Entry thereof is earnestly requested.

Priority

A copy of a certified copy the German patent application with the Serial No. DE 10303664.4, filed January 23, 2003 is enclosed herewith.

Drawings

A set of drawings in English language is enclosed herewith. Applicants respectfully submit that the revised set does not raise new matter. Withdrawal of the objection is respectfully requested.

Specification

A revised ABSTRACT is enclosed herewith, rendering the objection moot.

The objection of the specification for allegedly reciting trade names is respectfully traversed. Applicants' specification provides a detailed description of the various reagents and/or applications recited in the instant specification, including names and addresses of all the vendors and/or suppliers, which provide such tools/reagents. At the time the instant application was filed, the skilled worker was endowed with replete knowledge pertaining to reagents and/or applications recited in the specification. For e.g., the specification provides adequate description of HiTrap (available via Amersham Pharmacia Biotech), CentiPrep (available via Millipore, Inc.), MAXISORP, and other reagents which are useful for practicing the claimed invention in its broadest possible scope. The meaning(s) conveyed by these terms is generically understood in the filed of molecular biology. Withdrawal of the rejection is respectfully requested.

Regarding the use of subtitles, Applicants prefer not to use the PTO's suggested subtitles since these are merely "suggested for the applicant's use," and thus not mandatory. See, MPEP §608.01(a). Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶2

The Examiner is thanked for her careful review of the claims.

Claims 82 and 83 have been amended. The subject matter cancelled from amended claim 83 is now recited in new claim 108. No new matter is added.

As per the Examiner's suggestion, Applicants have amended claims 84 and 85 to recite US process claims. The rejection is therefore moot in view of the amendments. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §101

The Examiner is thanked for her suggestion, however, Applicants disagree.

It is respectfully submitted that the discrete amino acid sequences recited in claims 87 or 95, or combinations comprising such exist in nature. Therefore, the claimed recognition molecules comprising such sequences are clearly distinguished from naturally-existing molecules with respect to the primary structure. The Examiner is further invited to review the disclosure contained in Applicants' examples, wherein recognition molecules of the instant invention are obtained using recombinant techniques as opposed to extraction/purification from a natural source. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶1

The rejection of claims 77–86 under 35 U.S.C. §112, first paragraph as allegedly lacking is respectfully traversed.

Claims directed to molecules

The Office Action at page 7 contends that "the specification does not reasonably provide enablement for a recognition molecule comprising only 3CDRs in the heavy chain, or combinations of sequences of SEQ ID NOs: 33 and 35 or a method of preventing, diagnosing or treating tumor disease and/or metastasis." Applicants courteously disagree with this contention.

At the outset, it is respectfully submitted that Applicants' instant claims are drawn to recognition molecules comprising heavy chain CDR sequences (for example, polypeptides having the amino acid sequence set forth in SEQ ID NOs: 1, 3, 5) and light chain CDR sequences (for example, polypeptides having the amino acid sequence set forth in SEQ ID NOs: 7, 9, 11). See, Applicants' instant claim 87. Another set of recognition molecules, as recited in instant claim 95, is also based on this framework of heavy chain CDR sequences (for example, SEQ ID NOs: 2, 4, 6) and light chain CDR sequences (for example, SEQ ID NOs: 8, 10, 12). Together, the heavy and light-chain CDR regions comprise the structural elements of the claimed recognition molecules which impart the claimed functionality, for example, with respect to binding to a glycosylated MUC1 tumor epitope. In this regard, Applicants' specification expressly states that the sequences represent the binding domains and define the specificity of the recognition molecules. See, the paragraph bridging pages 9 and 10 of the originally-filed specification. Moreover, the ability of the above-mentioned framework sequences to afford structural and functional integrity to the claimed recognition molecules is not only widely-acknowledged in the field of immunology but is moreover consistent with Rudikoff's disclosure on antibody regions that are important mediators of antigen-binding. See, the paragraph bridging cols. 1 and 2 at page 1979 of Rudikoff et al.

The present application provides recognition molecules and methods of obtaining claimed molecules using techniques known in the art. The specification provides a detailed disclosure on antibody molecules comprising an antigen-binding site for the MUC1 tumor epitope and defines and distinguishes molecules which are specific against the glycosylated type. The instant claims recite both the structural as well as the functional aspects of the claimed molecules. The structural aspects of the claimed compounds are encompassed, for example, by the amino acid sequences provided in the sequence listing page. The functional aspects are encompassed, for example, by the claimed compounds' specificity of binding to the glycosylated MUC1 tumor epitope, whose structure is also provided (see, claims 113–116). In view of the disclosure provided and the mature state of the art, a skilled worker at the time the application was filed, could routinely identify variants of the recognition molecules which fall within the scope of the claims and retain the desired properties. For example, such molecules could be routinely screened and tested for the biochemical and pharmacological activity by utilizing techniques that are disclosed in the Examples.

The Office cited various references in the field of antibody engineering to contend that "it is expected that *all* of the heavy and light chain CDR in their proper order and in context of framework sequences which maintain their conformation…are required to produce a protein having antigen-binding function." The Office's reliance on Rudikoff to allege that "alteration of a single amino acid in the CDR region of phosphocholine-binding myeloma protein resulted in a loss of antigen-binding function" is misplaced. Firstly, Rudikoff (1982) is fully twenty years removed from the earliest priority date of the instant application (January, 2003) and thus fails to appreciate the progress made in antibody engineering during the post-genomic era. Even if Rudikoff were taken at face value, it is courteously submitted that the particular U4 variant of Rudikoff represents a *single inoperative embodiment* of phosphocholine-binding melanoma protein, which is used as a basis of the pending rejection. While highlighting this particular inoperative embodiment, the Office Action has neglected other operative embodiments that are characterized in Rudikoff. For example, in the DISCUSSION section at page 1982, Rudikoff expressly provides examples of such operative embodiments. Rudikoff also discusses the inherent bias in the methodology used in screening such variants, as it was specifically geared towards the identification of inoperative embodiments (i.e., variants with reduced/null binding activity):

> We have characterized another primary variant of S107 that has decreased antigen binding and a single amino acid substitution in the fifth residue of its J segment (39). However, it is clear that all such substitutions need not and probably do not affect antigen binding. For example, the heavy chain from the P-Cho-binding myeloma protein M167 (35) differs from that of S107 at 13 positions (8 in hypervariable regions including a size difference) and yet has an association constant for hapten only slightly lower than S 107. We have previously shown that, among anti-1,6-galactan-binding myeloma proteins, as many as eight or nine substitutions may occur in hypervariable regions with no significant effect on hapten affinity or specificity (13). Since these systems, as is the case of most hybridoma systems being examined today, are positively selected by antigen, they will in general reveal only substitutions not producing large changes in antigen binding. The negative selection used in this study permits analysis of changes that produce important phenotypic binding variation. (Emphasis added)

Applicants therefore respectfully submit that the reference supports enablement. It shows that eight or nine or 13 variations can be made with little effect on binding. Note the second sentence: "…all such substitutions need not and probably do not affect antigen binding." Moreover, as the Examiner's reference states, the screening technology routinely selects for applicable embodiments since antigen-based selection can be used. The authors *had to* employ a

methodology intended to look for inapplicable embodiments in order to find one. This clearly shows the routineness of the testing needed to arrive at successful variants with little or no inoperable embodiments. This firmly establishes enablement.

Even if the presence of inoperative embodiments within the scope of the claim posed a problem, this would not render the claim non-enabled. Inoperative embodiments are permissible within a claim. The standard for enablement is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); MPEP 2164.08(b). The specification provides clear guidance on how to isolate recognition molecules that fall within the scope of the claims. For example, the skilled worker could generate full-length antibody molecules having the immunospecificity and/or reactivity described in Applicants' specification, and use techniques of protein chemistry (for example, pepsin or trypsin digestion) to generate fragments of such molecules that are commensurate with the claims. Such methods are conventional. Alternatively, the skilled worker could rely on recombinant techniques, for example, art knowledge of cloning and/or phage display libraries to rapidly generate antibodies with slightly different structures and/or specificities compared to those derived from traditional approaches (for example, monoclonal antibodies). Such techniques are described in detail in Applicants' own specification. Based on the structures disclosed in Applicants' specification, any recognition molecule, for example, a polypeptide containing all the distinct domains and/or regions of an immunoglobulin molecule or a fragment thereof, which is immunospecific against molecules described herein (tumor MUC1 epitiope), could be routinely generated. Screening techniques based on for example, dissociation constants or neutralization studies, could be additionally utilized. This constitutes nothing more than routineness.

Claims directed to method of use

In the paragraphs spanning pages 11 to 16, the Office Action presents a lengthy discourse alleging that "*in vitro* studies do not reasonably correlate with *in vivo* effects," and thus Applicants' claims drawn to method of using the claimed molecules, especially in the medicinal and/or pharmaceutical applications are non-enabled. The publications of Dermer and Freshney are cited to support this contention. Applicants respectfully disagree with this contention.

Firstly, the PTO's reliance on Freshney et al. (*Culture of Animal Cells*, A Manual of Basic Techniques, 1983) and Dermer et al. (*Bio/Technology*, 1994) for the evaluation of the "state of the art" is rather misplaced insofar as the cited Freshney publication is fully twenty years before the earliest priority date of the instant application. The cited reference of Dermer is fully ten years before the earliest priority date. Given the rapid technological progress made in the post-genomic era, a skilled artisan would instantly question the applicability of such disclosure(s) for a fair and reliable estimate of the state of the art concerning Applicants' field of endeavor. The Office Action fails to convince why a skilled artisan would favor the disclosure(s) contained in these outdated publications over what is already described in Applicants' own specification. A skilled worker would only be inclined to do so if the instant specification was deficient in this regard. But as discussed *infra* it clearly is not.

Firstly, this rejection is deficient under controlling case law. It is by now well-settled that the initial burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention cannot be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, decades of scientific studies, both at the basic and clinical levels, have established that *in vitro* studies "reasonably correlate" with their *in vivo* counterparts. In this regard, the Examiner is cordially invited to review the attached copy of *Fiebig et al.*, European Journal of Cancer, 40 (2004) 802-820, showing correlation of *in vitro* to *in vivo* activity as the basis for anticancer drug discovery. There is no basis for the general allegation that "clinical correlations are generally lacking" to *in vitro* assays and/or cell-culture based assays.

Furthermore, the patent law is in accord with the realities of pharmaceutical arts.

In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), the court affirming the decision on reliance on *in vitro* data, and the decision stated that

> *in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

The court in *Cross* decision also noted the following

> Knowledge of the pharmacological activities of compounds is beneficial to the

> medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.
>
> ...
>
> Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. (Emphasis added)

The Federal Circuit in *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996), stated that

> all that is required is the test to be *reasonably indicative* of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Also, the court in *Brana* stated that

> it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The *Bundy* specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of §112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Thus, neither the reality of the pharmaceutical arts or industry or the state of the law in this area provide basis for the broad allegations on pages 12 and 16 of the Office Action. Thus, the rejection is without merit and should be withdrawn.

Regarding the allegation that the test described in the specification is *in vitro*, as established *infra*, this allegation is clearly without basis. Even if such allegations were true, it is by now well settled law that to establish the requisite objective enablement under the 35 USC 112, ¶1, an Applicants' disclosure is not required to present specific test results such as *in vivo* or *in vitro* test results. All that is required under the statute is objective enablement. See, e.g.,

Marzocchi et al., at 369:

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The MPEP is also in agreement with the holding in *Marzocchi*. The MPEP states that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

In any event, Applicants submit that the working examples (the *in vitro* data) provided herein "reasonably correlates" with the claimed invention, and in particular with the *in vivo* models described in the Examples. The specification provides sufficient guidance as to support the *in vitro* and *in vivo* effect of recognition molecules (or constructs thereof) against cancer cells and/or tumors. For example, Example 5 of present invention provides evidence that the recognition molecules of the instant invention specifically bind to the glycosylated MUC1 tumor epitope (i.e., using an ELISA assay). Example 6 demonstrates that the claimed recognition molecules specifically recognize a glycosylated MUC1 tumor epitope in a tissue substrate (using immunohistologic and immunocytologic staining techniques). The experimental data contained in these examples underscores the activity of the claimed molecules against the claimed targets, and use thereof, for example, in diagnostic assays (i.e., in the identification of tumors).

With respect to application of recognition molecules of the instant invention in the treatment of tumor diseases, Applicants' specification provides detailed guidance on how such molecules could be developed and used. In this regard, Example 7 describes synthetic strategies for the development of radio-labeled recognition molecules of the instant invention starting from a precursor molecule (i.e., an antibody). Example 8 demonstrates that such radio-labeled recognition molecules specifically recognize glycosylated MUC1 tumor epitope in numerous cancer cell-lines. Example 9 furthers this study in an *in vivo* mouse model, wherein the data convincingly demonstrates that constructs of the instant invention can be utilized *in vivo*. In Example 12, anti-tumor therapy of a Muc1-positive tumor using molecules of the instant invention is described using an *in vivo* mouse model. The study demonstrates that radio-labeled recognition molecules which specifically bind to the glycosylated MUC1 tumor epitope can be utilized for their anti-tumor properties. Efficacy studies, for example, comparing the anti-tumor effect of the recognition molecules of the instant invention with an irrelevant ^{90}Y-labelled

antibody (MOPC21), are also described.

Example 13 of Applicants' specification characterizes antibody-dependent cellular cytotoxic (ADCC) properties of the recognition molecules of the instant invention based on an *in vitro* model. The experimental data unequivocally show that the recognition molecules induce ADCC in cells which express the tumor epitope. A comparative assessment of the activity (i.e., cell-lysis) of the recognition molecules of the instant invention compared to other binding agents is further provided in Fig. 15.

Thus the representative examples and the scientific evidence disclosed therein objectively enable the use of the claimed recognition molecules and/or constructs/compositions thereof in a manner described Applicants' claims. Such detailed disclosure is more than sufficient to satisfy the statutory requirements under §112, ¶1. The Office Action fails to provide evidence with respect to why the claimed molecules could not be made and/or used in a manner described in Applicants' claims. The disclosure(s) contained in the Dermer, Freshney, and Gura references, which the Office Action uses as a basis to reject Applicants' claims, are especially weak in the face of the rich disclosure contained in Applicants' instant specification.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is no more than routine within the art. Withdrawal of the rejection under 35 U.S.C. §112, ¶1 is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Anthony J. Zelano/
Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410°

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Encl:
(a) Copy of a certified copy of the priority document
(b) Drawings
(c) Fiebig et al. European Journal of Cancer, 40 (2004) 802-820